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Original Article

Regional variability in the incidence of end-stage renal disease: an epidemiological approach

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Abstract

Background. Regional variability in the incidence of end-stage renal disease (ESRD) in Austria is reported. Our aim was to investigate the reason for low rates in the state of Tyrol.

Methods. ESRD incidence data were obtained from the Austrian Dialysis and Transplantation Registry. Additional sources were two health interview surveys, the Hospital Discharge Registry, the Mortality Registry and the Drug Wholesale Registry.

Results. Between 1995 and 1999, 4811 new cases of ESRD were recorded; the state of Tyrol (T) had a mean annual, age-adjusted incidence of 97.9/1 000 000 population [95% confidence interval (CI) 86.9–109.1], a number significantly lower than that for the rest of Austria [(RA), 120.9 (95% CI 116.9–124.5); $P < 0.001$]. This was due mainly to a difference in the incidence of ESRD patients with type 2 diabetes mellitus [(DM-2) T = 12.2 (95% CI 8.2–16.2) *vs* RA = 28.9 (95% CI 27.2–30.6); $P < 0.001$]. When these patients were excluded, the difference in the overall ESRD incidence disappeared. When data from various registries were analysed for the prevalence of DM, a highly significant correlation was found between ESRD incidence and DM.

Conclusion. We conclude that the variability in the ESRD incidence in Austria is explained mainly by regional differences in DM-2. Data from similar studies might be useful for predictions concerning resource allocation for ESRD programmes in the future.

Keywords: Austria; diabetes; end-stage renal disease; epidemiology; incidence

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Introduction

The first successful haemodialysis treatment of a patient with acute renal failure was performed by W. J. Kolff more than 50 years ago. Since then, medical advances have made this procedure a practical mode of therapy for chronic end-stage renal disease (ESRD). During the last two decades, a dramatic increase in the use of renal replacement therapy (RRT) has been observed worldwide [1,2], which has made the treatment of ESRD a significant public health burden in several developed countries [3]. The reason for this phenomenon is not entirely clear, but ageing of the population, improved overall survival and increase in numbers of patients at higher risk for the development of ESRD (e.g. diabetes and severe cardiovascular disease) may play a great role.

Even though the number of ESRD patients is increasing worldwide, a considerable regional variability has been reported [2–6], and a better understanding of this fact might help to develop preventive measures to reduce the burden of ESRD on a large scale and also facilitate advance allocation of health care resources. In contrast to the USA, where ethnic diversity greatly influences ESRD susceptibility [7], studies in more homogeneous populations might provide additional valuable information. The Austrian Dialysis and Transplantation Registry has reported areas such as the state of Tyrol with consistently low ESRD incidence [8]. Using this and other demographic databases, we attempted to test the following hypotheses, which could explain this observation:

(i) Real lower incidence, regional variability in the incidence of ESRD comparable with a variability in diseases that lead to ESRD.
(ii) Missed patients, e.g. by an insufficient diagnosis of renal disease.
(iii) Reduced patient/physician acceptance into RRT.

(iv) Lack of treatment facilities.
(v) Early patient death from other causes before RRT becomes necessary.

Subjects and methods

Data sources

The primary data source for our study was the Austrian Dialysis and Transplantation Registry [8]. Since 1964, this Registry, which is run by the Austrian Society of Nephrology, has been collecting data provided by the 64 dialysis and transplantation centres in Austria on all patients with ESRD treated for at least 3 months. New patients (regardless of whether initial therapy was haemodialysis, peritoneal dialysis or transplantation) between January 1, 1995 and December 31, 1999 were identified. The home address at commencement of ESRD therapy, which was identified in 97.5% of all cases, was used to locate the state of residence of each patient [Vienna (Vie), Lower Austria (LA), Upper Austria (UA), Styria (ST), Burgenland (B), Carinthia (C), Salzburg (S), Tyrol (T) and Vorarlberg (V)]. The mean ESRD incidence per year was calculated using the average of the 5-year study period for Tyrol and for all of Austria without Tyrol [rest of Austria (RA)].

The Austrian Dialysis and Transplantation Registry also receives data on the renal disease which led to ESRD. These diagnoses are grouped into eight categories which were used for analysis: vascular nephropathy, nephropathy associated with type 1 or type 2 diabetes mellitus, glomerulonephritis, kidney disease of unknown origin, interstitial nephritis/pyelonephritis, hereditary kidney disease and others (e.g. systemic lupus erythematosus, Goodpasture's syndrome, multiple myeloma, etc.).

The Austrian Federal Institute of Health provided information on the capacity of the dialysis centres in all nine Austrian states for the year 1998. Furthermore, the driving time between the patient's home address and the nearest dialysis facility was also calculated by the Austrian Federal Institute of Health [8].

The National Health Interview Survey (NHIS) covers the prevalence of chronic diseases, the extent of disability and the use of health care services. Data obtained during the 1991 [9] and 1995 [10] surveys were used.

The National Hospital Discharge Registry (NHDR) was screened for the years 1994–1998 to determine hospital admissions due to specific diseases using the International Classification of Diseases, Ninth Revision (ICD-9) [11]. Numbers are direct age-adjusted rates per million population (p.m.p.). In addition, data from the National Mortality Registry (MORT), which compiles and codes information on all deaths in Austria, was used for the years 1994 and 1995 [12].

From IMS-HEALTH AUSTRIA, one of the world's biggest market research institutions, data about the sale of specific categories of drugs (e.g. oral hypoglycaemic agents) in public pharmacies in each state were obtained (National Drug Wholesale Registry, provided by U. Scheithauer, IMS HEALTH AUSTRIA. Vienna, 2000). The numbers used herein represent units p.m.p. for the year 1999 (one unit corresponds to ~100–120 pills).

Data about the percentage of the population with a body mass index (BMI) > 30 were received from Kunze *et al.* [13].

Statistical analysis

Data are expressed as mean respective rates with a 95% confidence interval (CI).

For better comparability with other countries directly, age-standardized rates were computed according to the usual definition [14]. Age categories were defined as 0–14, 15–29, 30–44, 45–64, 65–74 and 75+ years. Weights were derived from the Austrian population in the year 1997. All computations were carried out with the SPSS programming language, which is suitable for computation of age-standardized rates (SPSS 10.0, SPSS Inc., Chicago, IL).

Significance tests for difference of age-standardized rates were based on Mantel–Haenszel score statistics [14]. We report the significance of rate differences by adapting the Bonferroni correction for the α-level which is known to be very conservative; therefore, we also present *P*-values.

Correlation between the incidence of ESRD due to type 2 diabetes mellitus (DM-2) and wholesale oral hypoglycaemic sales with respect to the percentage of the population with a BMI > 30 kg/m^2 was analysed by using a weighted linear regression model; weights were defined by population sizes. We report R^2-factor and *P*-value.

Results

Between January 1, 1995 and the end of December 1999, 4811 new cases of treated ESRD were recorded in Austria. Table 1 summarizes data on the number of new ESRD cases, the numbers for each age group

Table 1. Summary registration of ESRD incidence 1995–1999 in Tyrol and rest of Austria (RA)

State	No. of cases	Age category						Age-standardized incidence rate (95% CI) p.m.p.
		0–14	15–29	30–44	45–64	65–74	+75	
Tyrol	298	3 1%	23 7.7%	41 13.8%	101 33.9%	79 26.5%	51 17.1%	97.9 (86.8–109.1)
RA	4513	33 0.7%	176 3.9%	488 10.8%	1676 37.1%	1342 29.7%	798 17.7%	120.9 (117.4–24.5)*

*Significant *vs* Tyrol ($P < 0.001$, $P < 0.01$ after Bonferroni correction).

Table 2. End-stage renal disease incidence 1995–1999 according to primary renal disease in the rest of Austria (RA) and Tyrol (p.m.p.)

	RA	Tyrol	*P*-value
Total	120.9 (116.9–124.9)	97.9 (86.9–11.0)	0.001**
DM-2	28.9 (27.2–30.6)	12.2 (8.2–16.2)	< 0.001**
Vascular nephropathy	18.1 (16.7–19.5)	10.3 (6.6–14.0)	0.002*
Glomerulonephritis	16.8 (15.5–18.1)	15.3 (11.0–19.6)	0.589
Unknown origin	15.8 (14.5–17.1)	15.4 (11.0–19.8)	0.857
Interstitial nephritis	13.9 (12.7–15.1)	11.9 (8.1–15.7)	0.424
Hereditary kidney disease	8.6 (7.79–9.4)	6.5 (3.7–9.3)	0.197
DM-1	7.3 (6.4–8.2)	10.8 (7.2–14.4)	0.034
Others	11.2 (10.2–12.2)	13.7 (9.8–17.6)	0.204
Without DM-2	92.1 (89.0–95.2)	85.7 (75.7–95.7)	0.289

*$P < 0.05$, **$P < 0.01$ after Bonferroni correction.

and the mean annual age-adjusted incidence for Tyrol (T) and the rest of Austria (RA), which consists of all states with the exception of Tyrol.

As can be clearly seen, a large regional difference was observed, with an incidence rate of 97.9 (95% CI 86.8–109.1) in T in comparison with 120.9 (95% CI 117.4–124.5) for RA ($P < 0.001$, $P < 0.01$ after Bonferroni correction).

Additionally, we analysed the ESRD incidence rate for T and RA according to the main groups of renal diseases causing terminal renal insufficiency as defined by the Austrian Society of Nephrology (Table 2). There were significant differences with regard to the incidence of patients with DM-2 [T = 12.2 (95% CI 8.2–16.2) *vs* RA = 28.9 (95% CI 27.2–30.6), $P < 0.001$, $P < 0.01$ after Bonferroni correction] and vascular nephropathy [T = 10.3 (95% CI 6.6–14.0) *vs* RA = 18.1 (95% CI 16.7–19.5), $P = 0.002$, $P < 0.05$]. In contrast, other renal diseases had a similar frequency throughout Austria. When patients with DM-2 were excluded from the analysis, the incidence of ESRD patients was identical in T and RA [T = 85.7 (95% CI 75.7–95.7) *vs* RA = 92.1 (95% CI 88.9–95.1), $P = 0.289$].

From these data, we attempted to verify whether the low incidence of ESRD patients with DM-2 in Tyrol can be explained by a lower frequency of this disease in the general population. As can be seen from Table 3, each data source screened revealed a lower rate of diabetes mellitus in Tyrol as compared with the rest of Austria. Furthermore, we carried out

Table 3. Frequency of diabetes mellitus in Tyrol and the rest of Austria (p.m.p.)

County	NHIS 91	NHIS 95	NHDR	MORT	DRUG
Tyrol	11 830	13 000	3941	165	195 291
RA	16 790	24 220	4533	218	275 175

NHIS 91, National Health Interview Survey 1991; NHIS 95, National Health Interview Survey 1995; NHDR, National Hospital Discharge Registry 1994–1998; MORT, National Mortality Registry 1994–1995; DRUG, National Drug Wholesale Registry 1999, oral hypoglycaemic agents.

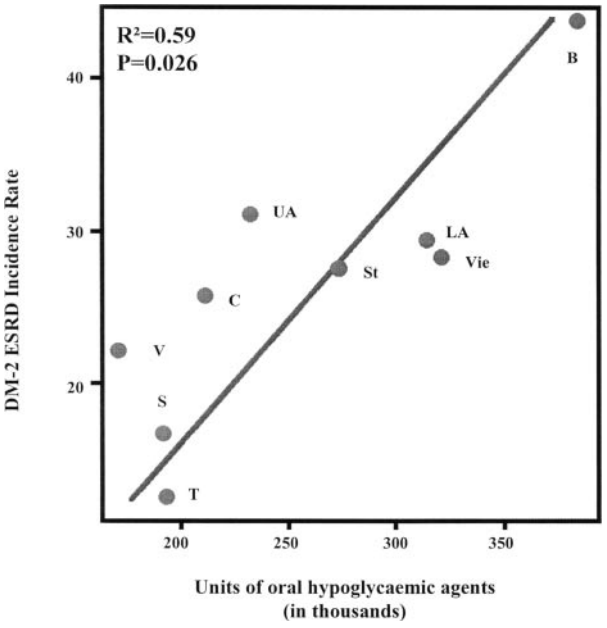

Fig. 1. Incidence of end-stage renal disease due to diabetes mellitus type 2 and wholesale oral hypoglycaemic sales in 1999 (p.m.p.) for Austria's nine states.

a weighted linear regression model between the ESRD incidence rate and the wholesale oral hypoglycaemic sales for each of the nine Austrian counties; for this an $R^2 = 0.59$, $P = 0.026$ was found (Figure 1).

When data on BMI for Austria were obtained from Kiefer *et al.* [13], a weighted linear regression between the prevalence of a BMI $> 30\,kg/m^2$ and the incidence rate of ESRD patients with DM-2 was also significant ($R^2 = 0.47$, $P = 0.041$) (Figure 2).

Discussion

Epidemiological studies have long been used to aid public health investigations by identifying geographic areas of elevated incidence of disease, from John Snows' cholera survey to recent investigations of cancer, stroke or myocardial infarction clusters. So far, only a few studies have dealt with the issue of

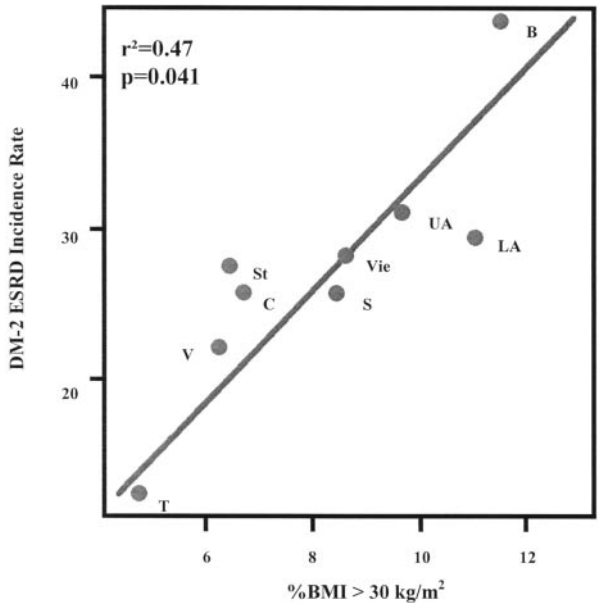

Fig. 2. Incidence of end-stage renal disease due to diabetes mellitus type 2 and percentage of the population with a BMI $> 30\,kg/m^2$ for Austria's nine states.

regional differences in the incidence of ESRD. Relman *et al*. [15], studying the US population, considered patient selection by doctors to be largely responsible for marked variations. Another study by Rosansky *et al*. [4] stratified the various states of the USA for differences in race, gender and age composition, and performed several regression analyses. This study mainly showed that states with relatively low rates of ESRD treatment tended to have fewer diabetic nephropathy cases, which was also suggested by two other studies [5,6].

The Austrian Dialysis and Transplant Registry consistently reports remarkable regional variability in new patients for RRT in Austria, a small country with a quite homogeneous population. The lowest incident patient rates are reported for Tyrol. It could be possible that the regional variability in ESRD is paralleled by a variability in the prevalence of diseases that lead to ESRD such as diabetes mellitus (real lower incidence). However, several other factors might also be involved such as missed patients due to failure to diagnose renal disease, patient or physician reluctance to accept RRT as a treatment option, a lack of dialysis facilities that would limit access, or early patient death before ESRD has developed.

Real lower incidence

As an initial step, we categorized the incident ESRD patient population in Tyrol and the rest of Austria according to eight main diagnostic groups as defined in the questionnaire drawn up by the Austrian Society of Nephrology, and this clearly showed that the observed difference was due mainly to a lower incidence of patients entering RRT with the diagnosis of DM-2. We then proceeded to evaluate whether the finding of a low prevalence of DM-2 is confined only to the dialysis population. As no diabetes registry is available in Austria, we had to rely on several other data sources, which included two National Health Interview Surveys (NHIS 1991 and 1995), the National Hospital Discharge Registry (NHDR), the National Mortality Registry (MORT) and the National Drug Wholesale Registry (DRUG). These registries provide estimates of the frequency of diabetes at different levels of the health care system. The National Health Interview Survey reports the participant's self-perception of disease. The National Drug Wholesale Registry covers patients receiving medication, the National Hospital Discharge Registry records patients discharged from hospitals with a specific ICD-9 code, and the National Mortality Registry identifies subjects suspected of having died from complications related to a disease. It was very convincing for us to find that all these different sources showed a uniform situation, with Tyrol having low rates of diabetes mellitus, e.g. the prevalence rate stated in the two National Health Interview Surveys gives a number of 11 831/p.m.p. for 1991 and 13 000 for 1995 for the Tyrolean population reporting diabetes, in comparison with the Austrian average of 16 787 (1991) and 24 216 (1995) (Table 3).

However, even though all these data show a picture of low diabetes rates in Tyrol, several limitations have to be mentioned. One might argue that the National Drug Wholesale Registry cannot be used to calculate the actual number of patients treated. As far as the results of our study are concerned, however, one would have to assume that patients in various parts of Austria are prescribed different numbers of pills for treatment of diabetes. This seems quite unlikely. Under-reporting of diabetes in all presented data could influence the result of our study, but we assume that this presents more a nationwide problem and thus should not affect state-specific differences. We are also aware of the potential pitfalls of diagnosing DM-2 nephropathy. In the majority of patients with DM-2, it is undoubtedly classical Kimmenstiel–Wilsons's glomerulosclerosis which leads to ESRD, but primary renal diseases such as glomerulonephritis, ischaemic nephropathy, etc. may occur more frequently than expected by chance. However, on the other hand, the prevalence of DM-2 probably could be underestimated.

How can we explain low diabetes rates in Tyrol? The prevalence of DM-2 is partly determined by genetic factors [16] but, unlike in the USA, where racial and cultural differences affect the incidence of ESRD [7], the Austrian population seems to be relatively homogeneous and no study until now has identified genetic isolation in Tyrol, an area where the majority of the population lives in mountainous areas.

On the other hand, obesity has been shown to be one of the most important factors triggering DM-2 [17]. Kiefer *et al*. [8] demonstrated a regional

variability in the distribution of subjects with a BMI > 30 kg/m^2 in Austria, which paralleled our data on DM-2-associated ESRD (Figure 2). The National Health Interview Survey of 1991 also showed Tyrol to be the state with the highest percentage of persons (50.8%) in Austria who take regular physical exercise [9].

Nonetheless, other factors might also contribute to a regional variability in RRT incidence, and we also tried to assess their importance.

Insufficient diagnosis

Insufficient diagnosis of renal disease in general might also influence RRT incidence, as suggested by several authors [6]. However, a search of the National Hospital Discharge Registry for diseases such as glomerulonephritis, nephritis and/or infectious kidney diseases showed the number of hospital stays in Tyrol (1560/year p.m.p.) to be identical to that for the rest of Austria (1562/year p.m.p.) ($P > 0.05$).

Reduced acceptance into RRT

Sekkarie *et al.* [18] suggested that the extent of co-morbidity could influence a physician's decision to refer a patient to RRT. The Austrian Dialysis and Transplant Registry collects data on patients who have undergone at least 3 months of RRT. If 'sick' patients were indeed excluded from RRT in Tyrol, one would expect the mortality rate for these 3 months to be much lower than in the rest of Austria. However, in Tyrol, 5.61% of ESRD patients die within 90 days of initiation of RRT, a figure similar to that observed in the rest of Austria (7.52, $P > 0.05$). Another hypothesis states that the distance to the nearest dialysis facility could affect patients' reluctance [19], but a study showed that almost all patients in Austria could reach a unit by car within 40 min [8].

Lack of facilities

Data obtained from the Austrian Federal Institute of Health demonstrate that dialysis capacity in Tyrol is much higher than in the rest of Austria [8], which excludes a lack of access to dialysis treatment due to limited health care resources. Additionally, since all costs for ESRD care in Austria are covered by public health insurance, we feel that socio-economic reasons cannot explain regional variabilities.

Early death

Finally, it has been suggested that patients die from other causes before reaching ESRD [20]. Data on cardiovascular mortality in general show that this rate in Tyrol is ~15% lower than the Austrian average [12].

The aim of the present study was to identify factors involved in the development of renal failure for possible use in a preventive programme. We show here that the low incidence of RRT in Tyrol can be explained mainly by low rates of DM-2. As the population in Tyrol has the lowest percentage of persons with a BMI > 30 kg/m^2 and the highest percentage taking regular physical exercise in Austria, our findings suggest that general health care preventive measures are able to reduce target organ diseases significantly.

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Conflict of interest statement. None declared.

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